UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF OHIO
WESTERN DIVISION

PAMELA RHEINFRANK, INDIVIDUALLY, AND AS PARENT AND NATURAL GUARDIAN OF M. D.	:	**Civil Action No. 1:13-cv-144**
PLAINTIFFS,	:	**Honorable Judge Susan J. Dlott**
ABBOTT LABORATORIES, ET AL.	:	
DEFENDANTS	:	

PLAINTIFFS PAMELA RHEINFRANK AND M.B.D.'s MOTION TO EXCLUDE IN PART PROFFERED EXPERT OPINIONS OF DR. KWAME ANYANE-YEBOA, DR. ANTHONY SCIALLI, DR. MAX WIZNITZER, AND DR. STEPHANIE GREENE, AND MEMORANDUM IN SUPPORT THEREOF

Respectfully submitted,

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PLAINTIFFS' MOTION TO EXCLUDE

Plaintiffs move the Court to exclude in part certain opinions of Defendants experts, Dr. Kwame Anyane-Yeboa, Dr. Anthony Scialli, Dr. Max Wiznitzer, and Dr. Stephanie Greene, pursuant to Federal Rules of Evidence 702, as interpreted in *Daubert v. Merrell Dow Pharm., Inc*. and its progeny.[1] This motion is supported by the accompanying Memorandum of Law.

MEMORANDUM OF LAW

I. INTRODUCTION

Defendants offer the opinion testimony of Dr. Kwame Anyane-Yeboa, Dr. Anthony Scialli, Dr. Max Wiznitzer, and Dr. Stephanie Greene to testify that: 1) Plaintiff M.B.D. suffers from Peters-Plus, an extremely rare genetic disorder with a one in a million occurrence rate, rather than from birth defects caused by Depakote; 2) the Depakote label contained adequate warnings; 3) Plaintiff M.B.D. does not have autism; and 4) Depakote does not cause Chiari I malformation. Because these proffered opinions are without reliable basis, are outside the expertise of the witness, or irrelevant, they must be excluded from evidence.

II. STATEMENT OF FACTS

Teratogens are substances such as medications, viruses or toxins that interfere with fetal development and cause birth defects. Plaintiffs allege that Depakote[2] causes severe birth defects, cognitive deficits and neurobehavioral delay to babies exposed in utero. Abbott sold Depakote, a potent teratogen, for decades, without adequate warning to protect unborn children from harm. Specifically, Abbott did not warn against prescribing the drug to women of childbearing years, did not instruct physicians to require pregnancy testing before prescribing Depakote, and did not mandate the use of contraception. Moreover, Abbott falsely equated the teratogenic risks of

[1] Plaintiffs note they have not filed *Daubert* motions on all of Defendants' experts, nor as to all opinions.
[2] The active ingredient in Depakote is divalproex sodium, which metabolizes to valproic acid. The terms Depakote and valproate or valproic acid are used interchangeably in the literature.

Depakote to that of all other antiepileptic drugs, and asserted in the label that the scientific literature could not be considered as proof of causation.[3] As a result, thousands of women were prescribed Depakote throughout their adult lives, including during pregnancy. Their children were exposed to Depakote in utero, often from the moment of conception until delivery, and many suffered devastating fetal malformations.

As confirmed in dozens of published articles, Depakote causes a wide array of major birth defects, including spina bifida, heart malformations, limb defects, oral clefts and numerous other anomalies.[4] As early as 1984 the term "fetal valproate syndrome" appeared in the medical literature to describe birth anomalies caused by in utero exposure to Depakote. In addition to major birth defects, Depakote also can cause characteristic facial abnormalities, such as a flat philtrum, thin upper lip with a vermilion border, broad or flat nasal bridge, short upturned nose, epicanthal folds, prominent forehead and micrognathia. Medical literature also confirms that Depakote causes significant developmental delay (meaning cognitive or behavioral deficits). Developmental delay is noted to be particularly prevalent among children who exhibit the facial features associated with fetal valproate syndrome.[5] Defendants' experts agree that 25% of all babies exposed to Depakote will suffer from birth defects or developmental delay. (Martin dep. 74:15-24, Doc.130, PageID15554; Yeboa dep. 52:13-24, Doc.81, PageID2360.) Further, while no safe dose of Depakote exists, over 30% of the children exposed to doses of 1100 mg of valproate or higher suffer from malformations.[6]

Unfortunately, Plaintiff Pamela Rheinfrank, took 1500 mg of Depakote a day throughout her pregnancy with minor Plaintiff M.B.D. to treat her epilepsy. It was apparent at birth that

[3] See 2003 Depakote Label, Ex. R to Pl's MSJ, Doc. 112-4, PageID 12715.
[4] A bibliography of articles describing birth defects caused by Depakote is attached as Ex A. For specific articles see Ex. 534, Doc. 86-2, PageID 4721, Ex. V & W to Pl's MSJ, Doc.112-7, PageID 12841-866.
[5] See Scialli dep. ex. 952, Doc.129-4, PageID15362.
[6] See Yeboa dep. ex. 948, Doc.81-2, PageID2696.

Plaintiff M.B.D. suffered numerous birth defects, including cloudy corneas, dysmorphic facial features, and skeletal anomalies. Shortly after birth, doctors diagnosed M.B.D. as having valproic acid embryopathy, which was confirmed by Dr. Howard Saal, a genetic specialist at Cincinnati Children's Hospital. (Saal Dep. 174:4-8, Doc.125, PageID14640.)[7] M.B.D.'s specific congenital anomalies are now known to include a defect of the eye known as Peters Anomaly (which required bilateral corneal transplant surgery in order to restore some level of visual acuity), Chiari I malformation, (which required brain surgery in order to lift a protrusion of the cerebellum from the spinal canal), microcephaly, facial dysmorphisms, urteropelvic junction obstruction, hypotonia, joint laxity and developmental delay.[8] Although a Social Security report initially indicated that M.B.D. suffers from autism spectrum disorder, her treating physicians have not confirmed the diagnosis and Plaintiffs therefore do not allege autism in this case.

III. LEGAL STANDARD

Federal Rule of Evidence 702 and the principles the Supreme Court articulated in *Daubert v. Merrell Dow Pharmaceuticals, Inc*. establish the admissibility standards for expert opinions. Pursuant to Rule 702, an expert offering an opinion must be "qualified by knowledge, skill, experience, training, or education." Fed. R. Evid. 702. If the proffered testimony meets that basic threshold, then it must meet four additional requirements:

> (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;
> (b) the testimony is based on sufficient facts or data;
> (c) the testimony is the product of reliable principles and methods; and
> (d) the expert reliably applies the principles and methods to the facts of the case.

Fed. R. Evid. 702. In the seminal case of *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, the Supreme Court instructed that the district court must act as a "gatekeeper" to ensure that

[7] Valproic acid embryopathy is the same diagnosis as fetal valproate syndrome.
[8] See Ex. B to Pls' MSJ, Doc.114, PageID13801, a portion of Plaintiff M.B.D.'s medical records.

"scientific testimony is both relevant and reliable." *Daubert*, 508 U.S. 579, 589 (1993). The proponent bears the burden of satisfying this two part inquiry by a "preponderance of proof." *Decker v. GE Healthcare Inc*., 770 F.3d 378, 391 (6th Cir. 2014) citing *Sigler v. Am. Honda Motor Co*., 532 F.3d 469, 478 (6th Cir. 2008).

The requirement under Rule 702 that the expert's opinion must help the trier of fact to understand the evidence or to determine a fact at issue "has been interpreted to mean that scientific testimony must 'fit' the facts of the case, that is, there must be a connection between the scientific research or test result being offered and the disputed factual issues in the case in which the expert will testify." *Pride v. BIC Corp.*, 218 F.3d 566, 578 (6th Cir. 2000). Expert testimony that is unrelated to an issue in the case is not relevant and therefore unhelpful to jurors. *Daubert*, 508 U.S. at 591 (citation omitted).

In addition to relevance, Rule 702 assumes "the expert's opinion will have a reliable basis in the knowledge and experience of his discipline." *Daubert*, 508 U.S. at 592. When examining the qualifications of the expert, the court does not view the expert's qualifications in the abstract, but rather asks "whether those qualifications provide a foundation for a witness to answer a specific question." *Berry v. City of Detroit*, 25 F.3d 1342, 1351 (6th Cir. 1994).

Experts must base their opinions upon reliable methodology. *See Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 154-55 (1999). Courts must assure that the expert "employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Id.*, 526 U.S. at 152. To determine whether the methodology is reliable, *Daubert* requires consideration of four factors: whether the opinion is confirmed by testing, whether it has been subject to peer review, whether a known error rate exists, and the "acceptability" of the opinion by the scientific community. *Daubert*, 508 U.S. at 145. These four *Daubert* factors are

not exhaustive, and the gatekeeping inquiry must be tied to the particular facts. *Id.* at 150. The court must determine whether the expert's testimony reflects scientific knowledge, whether the findings are derived from the scientific method, and whether the work product reflects good science. *Smelser v. Norfolk So. Ry*. Co., 105 F.3d 299, 303 (6th Cir. 1997).

Expert testimony must also be excluded if it is contrary to law. *See In re Gandolinium-Based Contrast Agents Prods. Liab. Litig.*, No. 1:08-GC-5000, 2010 U.S. Dist. LEXIS 43444 *111-12 (N.D. Ohio May 4, 2010). Testimony that is contrary to law is inherently unreliable and offers no assistance to the jury.

IV. ARGUMENT

A. Motion To Exclude The Testimony Of Dr. Kwame Anyane-Yeboa

Plaintiff M.B.D. has been diagnosed with several birth defects, including an anterior chamber defect of the eye called Peters Anomaly. Her treating geneticist Dr. Saal attributes all her birth defects, including Peters Anomaly, to Depakote. Abbott's expert, Dr. Yeboa, opines instead that Plaintiff has a genetic syndrome called Peters-Plus. Plaintiffs move to preclude Dr. Yeboa's opinions concerning Peters-Plus as unreliable.

1. Dr. Yeboa's Definition Of Peters-Plus Is Unsupported

Peters-Plus is a rare genetic condition with a 1 in 1,000,000 occurrence rate. (Yeboa dep. at 77:1-10, Doc.81, PageID2366). Peters-Plus is characterized by "developmental defects in the anterior chamber of the eye, a typical face, clefting, short limb dwarfism and developmental delay."[9] "Most cases have prenatal growth retardation, and virtually all cases are disproportionally short postnatally. Arms and legs are equally shortened…"[10] Dr. Saal, who is familiar with Peters-Plus and in fact has published on the syndrome, testified unequivocally that

[9] See Yeboa Ex. 939, Doc.81-2, PageID2637, Liesbeth J.J.M. Mailette de Buy Wenniger-Prick, et al., The Peters' plus syndrome: a review, Annales de Genetique, 45 (2002) 97-103.
[10] Ex. 939, Doc. 81-2, PageID2637.

M.B.D. does not have Peters-Plus. Simply put, "she is not a dwarf." (Saal dep. 132:19-133:18, Doc.125, PageID14629). Moreover, she lacks many of the other features, such as cardiac malformations, cleft lip and palate, small, malformed ears, short wide hands, fifth finger clinodactyly and Cupid's bow upper lip.[11] Although a mutation of the B3GALTL gene has been identified for Peters-Plus,[12] Dr. Saal rejected genetic testing for this mutation as unnecessary based on M.B.D.'s clinical presentation. (*Id.* at 132:19-133:12, Doc.125, PageID14629.)

Despite the fact that M.B.D. is not a dwarf, and lacks many other characteristics that define the syndrome, Dr. Yeboa opines that M.B.D. has Peters-Plus caused by a genetic mutation. In providing this opinion, Dr. Yeboa created his own definition of Peters-Plus in which he modified both the clinical features and responsible gene, thereby contradicting the entire body of published medical literature. Dr. Yeboa's personal definition of Peters-Plus rejects the consensus that Peters-Plus consists of: "developmental defects in the anterior chamber of the eye, a typical face, clefting, short limb dwarfism and developmental delay."[13] Instead of accepting these specific traits, Dr. Yeboa testified: ". . . Essentially, when we say Peters-Plus, you are referring to patients who have Peters anomaly plus something else, okay." (Yeboa dep. 76:5-7, Doc.81, PageID2366.) No published literature supports this overly broad contention.

In regard to genetic testing, Dr. Yeboa disagrees that a normal finding for the B3GALTL gene would exclude Peters-Plus. Instead, he speculates that even if genetic testing showed that M.B.D. did *not* have the B3GALTL mutation, then some other mutation of a different gene

[11] See Saal Ex. 2, Doc.124-1, PageID14526, Saal Rebuttal Report.

[12] See Yeboa Ex.942, Doc.81-2, PageID2659, Oberstein, et al. Peters Plus Syndrome is Caused by Mutations in B3GALTL, a Putative Glycosyltransferase, Am. J. Human Genetics, Vol. 79, 562-66 (Sept. 2006).

[13] Ex. 939. In addition to these features, Wenniger-Prick, et al., notes that short broad hands were reported in 100% of patients with Peters-Plus; a cupid bow upper lip is present in 98% of patients with Peters-Plus; short limbs are reported in 95% of patients with Peters-Plus and other features such as cleft lip/palate, a broad and sometimes webbed neck, and ear malformations are common. M.B.D. does not have such features. See Saal Ex. 2, Doc.124-1, PageID14527, Saal Rebuttal Report.

would be found if whole genome sequencing were conducted, and then that gene would be presumed to be the basis for diagnosing Peters-Plus. (*Id.* at 220:13-18, Doc.81, PageID2402.) Of course, Dr. Yeboa cannot identify which gene this would be, or provide any scientific basis or support for his claim that any gene mutation found in M.B.D. would be responsible for her Peters Anomaly and other birth defects and constitute Peters-Plus. (*Id.* at 220:13-221:12, Doc.81, PageID2402.)

Dr. Yeboa's opinion, in effect, morphs Peters-Plus from a well described genetic syndrome with known physical characteristics and an identifiable gene mutation, into a sweeping, catch all syndrome involving every case of Peters Anomaly and every possible genetic mutation. Clearly, this theory has not been tested, published or subject to peer review, but rather was created solely for litigation. Dr. Yeboa's opinions regarding an alleged diagnosis of Peters-Plus lack sound methodology and must be excluded as misleading and unreliable.

2. Dr. Yeboa's Opinion That Genetic Testing To Exclude Peters-Plus Is Required Before Diagnosing The Cause Of Plaintiff's Injuries Is Unreliable

Dr. Yeboa acknowledges that Peters-Plus is extremely rare, with an estimated 1 in 1,000,000 occurrence rate. (*Id.* at 77:1-10, Doc.81, PageID2366). He also acknowledges that the risk of fetal malformations from maternal ingestion of 1500 mg. of Depakote a day exceeds 30%. (*Id.* at 201:21-202:4, Doc.81, PageID2397). Yet he opines that genetic testing to exclude Peters-Plus must be conducted before diagnosing valproate teratogenicity. He states: "I am aware of no reasons why such testing [DNA whole-exome sequencing] cannot or should not be undertaken and a sound differential diagnosis of the cause of M.B.D.'s birth defects requires that such testing be undertaken."[14] In addition to disregarding the fact that M.B.D. lacks the physical traits of Peters-Plus, Dr. Yeboa also disregards the math. Namely, he contends that before one

[14] See Yeboa Ex.936, Doc.81-1, PageID2573.

can conclude that a child was injured by a drug with a 30% risk of birth defects, one must first exclude a 0.0001% chance that the cause is genetic.

Dr. Yeboa's approach defies rationality analysis. Before excluding a potential cause under a differential diagnosis, there must be a rational basis to consider it in the first place. The Sixth Circuit recognizes that a doctor's differential diagnosis is reliable where the doctor (1) "objectively ascertains, to the extent possible, that nature of the patient's injury, (2) ***'rules in'*** one or more causes of the injury using a valid methodology, and (3) engages in 'standard diagnosis techniques by which doctors normally rule out alternative causes' to reach a conclusion as to which cause is most likely." *Best v. Lowes Home Ctrs, Inc.*, 563 F.3d 171, 179 (6th Cir. 2009) (emphasis added), citing *In re Paoli Railroad Yard PCB Litigation*, 35 F.3d 717 (3d Cir. 1994). Here, Dr. Yeboa has no reliable methodology to "rule-in" Peters-Plus. Neither the clinical presentation of M.B.D. nor the statistical odds of Peters-Plus support consideration of this diagnosis. When faced with a 30% incidence rate of birth defects with Depakote compared to a 1 in 1,000,000 chance of a genetic cause, which easily can be excluded by a mere visual assessment, opining that genetic testing must be done does not constitute reliable testimony.

Dr. Yeoba's approach is the medical equivalent of a fishing expedition. Medical tests are only ordered (and permitted by insurance companies) when medically indicated. As the Sixth Circuit recognized in *Best*, "doctors need not rule out every conceivable cause in order for their differential-diagnosis-based opinions to be admissible." *Best*, 563 F.3d at 181; *See also, Heller v. Shaw Indus., Inc.*, 167 F.3d 146, 156 (3rd Cir. 1999). Dr. Yeboa's opinion that whole genome sequencing is required before providing an opinion on causation contradicts the law and medical practice, and therefore must be excluded.

B. Motion To Exclude Opinions Of Dr. Anthony Scialli

Defendants' expert Dr. Scialli is an OB/GYN and toxicologist who was a former president of the Teratology Society. Oddly, he will offer no opinions on the teratogenicity of Depakote in this case, including no opinion on whether Depakote causes Peters anomaly or Chiari I malformation. Instead, Abbott offers Dr. Scialli to testify about genetics (Peters-Plus), Depakote labeling, and Abbott's regulatory compliance. Dr. Scialli lacks the appropriate qualifications and/or basis to opine on these issues. Therefore, his testimony must be excluded.

1. Dr. Scialli Is Not Qualified To Diagnose Peters-Plus

Dr. Scialli opines that Plaintiff M.B.D. has Peters-Plus.[15] However, Dr. Scialli is not a geneticist, dysmorphologist, or even a pediatrician, and has no qualifications to diagnose Peters-Plus. It is well recognized that "[a]n expert may not testify beyond the scope of his or her expertise, and holding a medical degree 'is not enough to qualify [a doctor] to give an opinion on every conceivable medical question.'" *In re Heparin Prods. Liab. Litig.*, 803 F. Supp 2d 712, 747 (N.D. Ohio 2011). While a doctor need not be a specialist in the exact area of medicine implicated, the doctor must have some "specialized knowledge as a result of training or experience relevant to the opinions he offers." *Id.* at 747.

Dr. Scialli does not treat children or diagnose them with common disorders, much less extremely rare genetic disorders, like Peters-Plus. (Scialli dep. 25:2-16, Doc.129, PageID15156). Dr. Scialli admits that diagnosing genetic conditions is outside his area of expertise, and that he has never been responsible for examining an infant to determine if the child has fetal abnormalities.[16] (*Id.* at 24:7-26:10, Doc.129, PageID15156). Dr. Scialli has never seen a person with Peters Anomaly, nor been called in to treat a person with Chiari malformation. (*Id.* at

[15] See Scialli Ex. 950, Doc.129-1, PageID15249.
[16] Dr. Scialli does perform circumcisions. (Scialli dep. 25: 2-5, Doc.129, PageID15156).

25:14-24, Doc.129, PageID15156). Dr. Scialli has never diagnosed a child with fetal valproate syndrome or Peters-Plus. (*Id.* at 80:24-81:5, Doc.129, PageID15170.) Moreover, Dr. Scialli has never even seen the Plaintiff; he admits he has never examined M.B.D. and did not rely on any photos of M.B.D. in reaching his opinions. (*Id.* at 123:15-124:5, Doc.129, PageID15181.) Dr. Scialli therefore opines outside his area of expertise, as to a disorder he has never seen or diagnosed, and as to a patient he has never seen or examined. Such testimony is unreliable and inadmissible. *In re Welding Fumes Prods. Liab. Litig.*, 1:03-cv-17000, 2010 U.S. Dist. LEXIS 146067, *248 (N.D. Ohio, June 4, 2010).

Dr. Scialli claims to base his opinion upon literature he has read about symptoms of Peters-Plus and Fetal Valproate Syndrome, and upon his experience as an OB/GYN. (Scialli dep. 83:2-4, Doc.129, PageID15171). However, "a person does not become an expert in an area outside of his regular field by merely 'reading up' for the specific purpose of testifying." *In re Welding Fumes*, 2010 U.S. Dist. LEXIS at *188. Dr. Scialli's inexperience with Peters-Plus is evident: he admits that he does not know the difference between a thin or long upper lip and a Cupid's bow upper lip, the first of which is characteristic of fetal valproate syndrome while the latter is present in 98% of individuals with Peters-Plus syndrome. (*Id.* at 87:12-88:5, Doc.129 PageID15172.) He acknowledged his expert report incorrectly states that epicanthal folds are "almost invariably noted in fetal valproic syndrome, but are not reported in Peters-Plus," when in fact only 14% of the Depakote exposed children in the study he cited had epicanthal folds. (*Id.* at 105:16-106:24, Doc.129, PageID15176). Dr. Scialli is clearly outside his area of expertise opining that Plaintiff M.B.D. has Peters-Plus and his testimony must be excluded.

2. Dr. Scialli Lacks A Reliable Basis To Opine That The Label Is Adequate

Dr. Scialli opines: "the FDA-approved Depakote labeling contained adequate and

scientifically justified warnings about the use of Depakote during pregnancy."[17] However, Dr. Scialli disavowed having an opinion as to whether Depakote causes birth defects. He testified that he was not offering an opinion on causation at trial and that he not reviewed the literature to conduct a causation analysis. (*Id.* at 37:22-39:14; 46:2-47:1, Doc.129, PageID15159, 15162.) Because Dr. Scialli has no opinion on causation, he has no basis upon which to determine if the warning in the label was adequate. Therefore his testimony regarding the label must be excluded.

A drug label warning is adequate if it reasonably discloses all risks inherent in the use of the drug which the manufacturer knew or should have known to exist. *Reece v. Astrazeneca Pharms., LP*, 500 F. Supp. 2d 736, 749 (S.D. Ohio, 2007), *citing Seley v. G.D. Searle & Co.*, 423 N.E.2d 831 (Ohio 1981). The adequacy of a warning is measured by what is stated, as well as the manner in which it is stated. *Reece*, 500 F. Supp. 2d at 749. "A reasonable warning not only conveys a fair indication of the nature of the dangers involved, but also warns with the degree of intensity demanded by the nature of the risk." *Id.* Dr. Scialli's methodology, in which he purports to judge the warning adequate when he in fact has no opinion as to what the risk actually is, cannot be considered sound. Therefore his testimony on the adequacy of the label must be excluded.

3. Dr. Scialli's Opinions Concerning Regulatory Compliance Are Contrary To Law And Must Be Excluded As Unreliable

Dr. Scialli offers opinions that "with respect to its FDA-approved product, valproic acid, Abbott complied with FDA requirements," and "safety information regarding pregnancy supplied by the manufacturer (Abbott) to the FDA was adequate and appropriate."[18] These opinions are beyond his expertise, unsupported by an adequate basis, and contrary to law.

[17] Scialli Ex. 950, Doc.129-1, PageID15249.
[18] Scialli Ex. 950, Doc.129-1 PageID15249.

Dr. Scialli testified that his only expertise in regard to FDA regulatory matters was limited to pregnancy, fertility and lactation labeling requirements. (Scialli dep. 179:16-180:2, Doc.129, PageID15195.) He has never been an employee of a drug company, worked in a drug regulatory department, or worked as a regulatory employee of the FDA. (*Id.* at 167:23-168:24, Doc.129, PageID15192.) Throughout his deposition, Dr. Scialli could not point to a single specific federal regulation concerning drug companies beyond specific pregnancy labeling issues. (*Id.* at 149:4-8; 215:15-21, Doc.129, PageID15187, 15204.) Dr. Scialli could not define the components of a pharmacovigilance plan, was not aware of a company's obligation regarding adverse events (other than the requirement that they must be submitted to FDA), was unaware if any drugs had ever been removed from the market based solely on adverse events, and was not familiar with the term "safety signal." (*Id.* at 148:19-151:15, Doc.129, PageID15187.) He had no opinion on what a drug company should do in regard to comparing adverse event reports to historic rates. (*Id.* at 153:24-154:6, Doc.129, PageID15188.) He was not familiar with the FDA Guidance on disproportionality analysis of adverse events, and was unfamiliar with terms such as EB05 and PRR. (*Id.* at 154:23-156:2, Doc.129, PageID15189.) He agreed he had no opinion to offer in regard to Abbott's data mining activities. (*Id.* at 156:18-22, Doc.129, PageID15189.)

Further, he did not rely upon any deposition testimony of any Abbott employees in forming his opinion that Abbott complied with FDA requirements. (*Id.* at 156:24-157:4, Doc.129, PageID15189.) He did not know if Abbott employees had identified a signal for developmental delay or autism in their adverse event database for Depakote. (*Id.* at 157:5-9, Doc.129, PageID15189.) He claims that Abbott provided adequate safety information to the FDA, but he did not review the 2005 Prior Approval Supplement to determine what information had been omitted; he never compared the final report with the original draft. (*Id.* at 182:7-186:5,

Doc.129, PageID15196.)

As to drug company responsibilities, he claimed he did not know if there was a regulatory prohibition upon drug companies initiating their own safety studies. (*Id.* at 157:10-15, Doc.129, PageID15189.) (Obviously, there is not.) He repeatedly denied that a manufacturer has an obligation to assure product safety, and instead postured that the only obligation of a drug company is to report potential safety issues to FDA and then wait for instructions. (*Id.* at 212:3-24, Doc.129, PageID15203.) When questioned regarding who bears the primary responsibility for drug labeling, Dr. Scialli continuously qualified his answers, claiming that the manufacturer and FDA "together bear responsibility for the labeling" and that "the labeling is always subject to FDA approval." (*Id.* at 173:4-9, Doc.129, PageID15194.) This conflicts with the Supreme Court's opinion in *Wyeth v. Levine*, which established that the manufacturer has complete control over its label to add updated safety information at any time and expressly rejected the manufacturer's argument that "the FDA, rather than the manufacturer, bears primary responsibility for drug labeling." *Wyeth*, 555 U.S. at 570. The Supreme Court even noted that Defendant's argument that FDA bears primary responsibility for the labeling "Misapprehends . . . the federal regulatory scheme." *Id.* at 570.

In short, beyond pregnancy labeling, Dr. Scialli has no understanding of FDA regulations upon which to base his omnibus opinion that "Abbott complied with regulatory requirements," nor does he have any factual support for his opinion. Further, his understanding of the manufacturer and FDA's responsibility for drug safety is contrary to law, and therefore misleading to the jury. Dr. Scialli's omnibus regulatory opinions must therefore be excluded. *See In re Gandolinium-Based Contrast Agents Prods. Liab. Litig.*, 2010 U.S. Dist. LEXIS 43444 at *109-112 (court excluded expert testimony on FDA drug approval and labeling process as it

was contrary to the law in *Wyeth v. Levine*).

Dr. Scialli also opines in his report that prior to Plaintiff M.B.D.'s birth, "FDA did not require or even request that Abbott engage in a pregnancy registry or perform additional studies with respect to the possible pregnancy effects of valproic acid." Such an opinion implies that a manufacturer has no independent responsibility to assure the safety of its drugs, and further implies that FDA had the authority to require manufacturers to perform additional studies in the years prior to 2004. Both propositions are contrary to law. Manufacturers are always responsible for the safety of their products, and must undertake studies of their drugs when warranted by new evidence. *Wyeth*, 555 U.S. at 570-71; 21 CFR § 314.81. Further, the FDA did not gain the authority to require a manufacturer to conduct additional studies until the Food and Drug Administration Amendments Act (FDAAA)[19] became effective on March 25, 2008.[20] This fact was affirmed in *Wyeth.* Dr. Scialli's opinion that FDA did not require or even request additional studies is misleading and should be excluded as unreliable. *See Wyeth*, 555 U.S. 555 (2009).

C. Motion To Exclude The Testimony Of Dr. Max Wiznitzer

Plaintiffs move to preclude Dr. Wiznitzer from testifying about: (1) the adequacy of the labeling; and (2) that M.B.D. does not have autism.

1. Dr. Wiznitzer's Opinion On The Adequacy Of The Label Is Unreliable

a. Dr. Wiznitzer Has No Opinion On Causation And Has Failed To Review The Published Literature On Depakote Teratogenicity

As with Dr. Scialli, Dr. Wiznitzer offers an opinion on the adequacy of the warning in the label without first having formed an opinion as to whether Depakote causes birth defects. (Wiznitzer dep. 12:8-12, Doc.128, PageID15011). He specifically denies having any opinion on causation. *Id.* He has not reviewed any published studies on Depakote and birth defects and is

[19] See Public Law 110-85-Sept. 27, 2007.
[20] 21 U.S.C. § 355(o).

not familiar with the warnings in the current label. (*Id.* at 10:19-23; 46:11-47:9, 70:6-14, Doc.128, PageID15011, 15020, 15026.) The adequacy of a drug label is measured by the risks disclosed, what is stated, and the manner in which it is stated. *Reece*, 500 F. Supp. 2d at 749. As previously discussed, no basis exists to evaluate the adequacy of the warning when the expert has no opinion on the nature and extent of the risks at issue. With no opinion on causation and no reliance on any published studies, Dr. Wiznitzer has no basis to opine about the adequacy of the warning.

Dr. Wiznitzer purports to base his opinion about the adequacy of Abbott's warning on a comparison of the label to three articles concerning "consensus guidelines" for prescribing antiepileptic drugs.[21] These guidelines allegedly represent what was known by neurologists at the time about which drugs to prescribe during pregnancy. However, the standard for determining the adequacy of the warning is based upon what the drug manufacturer knew or should have known, not on what doctors knew at the time. *Reece*, 500 F. Supp. at 749. The law does not reward the non-curious drug company by providing a defense based on inaction. Therefore the opinion of Dr. Wiznitzer, which is based upon what doctors allegedly knew at the time, is not helpful to the jury and lacks a reliable basis as it does not address what was known or should have been known by Abbott.

2. Dr. Wiznitzer's Testimony About The Knowledge Of The Entire Medical Community Is Speculative

Dr. Wiznitzer also opines on the alleged understanding of every prescribing doctor in the United States, based on his interpretation of the Depakote label and consideration of the three

[21] Delgado-Escueta, et al., Consensus guidelines: Preconception counseling, management, and care of the pregnant woman with epilepsy, Neurology 1992; 42 (suppl. 5): 149-160; Practice parameter, Management issues for women with epilepsy (summary statement), Report of the Quality Standards Subcommittee of the American Academy of Neurology, Neurology 1998; 51: 944-948; Meador, Neurodevelopmental effects of antiepileptic drugs, Current Neurology and Neuroscience Reports 2002, 4: 373-378.

published "consensus guidelines" for prescribing AEDs.[22] (Wiznitzer dep. 10:19-23; 36:12-24; 40:10-13 Doc.128, PageID15011, 15017-18.) No basis exists to assume that every neurologist in the United States, much less every general practitioner, internist, or nurse practitioner, read or relied upon these articles, or interpreted them in the same way as Dr. Wiznitzer. Courts routinely exclude expert testimony as to the general knowledge in the medical community. As the court in *Pfizer Inc. v. Teva Pharms USA, Inc.*, explained, although a physician may have 20 years of experience in the field and prescribe the drug, that does not qualify him as an expert "about what all doctors generally consider when making prescription decisions;" nor can he testify "as to all physicians' understandings of the risks and benefits" of the drug. *Pfizer*, 461 F. Supp. 2d 271 (D.N.J. 2006). *See also, Bartlett v. Mut. Pharm. Co.*, 742 F. Supp. 2d 182 (D.N.H. 2010) (court granted plaintiff's motion to exclude expert testimony that doctors generally know about SJS/TEN and their link to NSAIDS because such testimony was speculative and the expert physician failed to identify a reliable basis for such testimony); *In re Baycol Prods. Litig.*, 532 F. Supp. 2d 1029, 1069 (D. Mn. 2007) (court held that expert physician could not provide expert testimony "as to what other physicians knew or would have done with different information."); *In re Rezulin Prods. Liab. Litig.*, 309 F. Supp. 2d 531 (S.D.N.Y. 2004) (court excluded expert testimony regarding physicians' practices of reading drug labels and the understanding of such labels as such testimony was speculative).

Moreover, this testimony is completely irrelevant. The prescriber in this case was not a neurologist, but rather an internal medicine resident at an outpatient clinic at Good Samaritan Hospital. Although he tries to cover the waterfront, Dr. Wiznitzer cannot speak on behalf of what every doctor in the United States knew, much less what every resident in training knew, particularly when the actual prescriber has made clear she did not know the information bandied

[22] *See* articles in footnote 21.

about by Dr. Wiznitzer as common knowledge. (Lemus dep. 19:2-14, 23:8-12, Doc. 83, PageID 3260, 3261.)

Further, Dr. Wiznitzer has no empirical evidence that the 2003 labeling for Depakote was adequate to warn physicians of the nature and scope of the teratogenic risks of the drug. Dr. Wiznitzer did not conduct any surveys, focus groups, or interviews of any physicians to determine whether prescribing physicians found the warning to be adequate. (Wiznitzer dep. 38:4-17; 58:10-19; 60:1-12, Doc.128, PageID15018, 15023.) He claimed to speak for all neurologists in the United States, but did not speak to a single neurologist in forming his opinion. The court in *Calisi v. Abbott Labs* was faced with a similar lack of empirical evidence and found that such an omission was fatal to whether an expert witness was permitted to testify to the jury. *Calisi*, No. 11-10671-DJC, 2013 U.S. Dist. LEXIS 139257 at *23-36 (D. Mass., Sept. 27, 2013).

Dr. Wiznitzer also lacks a sufficient basis for his opinions regarding the adequacy of the warning label because he failed to consider the scientific literature, Abbott documents, employee depositions, FDA documents, and subsequent labeling changes. (Wiznitzer dep. 10:19-23; 11:5-23; 23; 28:6-15; 46:16-47:9; 70:6-14, Doc.128, PageID15011, 15015, 15020, 15026.) This is the opposite of the situation in the Gadolinium cases, in which the court permitted an expert, who had in fact reviewed the published studies, internal documents and company studies, to testify as to the adequacy of the warning. *In re Gadolinium-Based Contrast Agents Prods. Liab. Litig.*, 2010 U.S. Dist. LEXIS 43444 at *74-76.

3. Dr. Wiznitzer's Opinion Regarding Autism Is Irrelevant

Dr. Wiznitzer opines that he does not believe Plaintiff M.B.D. has autism or autism spectrum disorder. (Wiznitzer dep. 12:21-25, Doc.128, PageID15011.) Plaintiff's treating doctors have not diagnosed her with autism or autism spectrum disorder. Although an earlier

report from a Social Security disability examination did contain such a diagnosis, it has not been confirmed by her physicians at Cincinnati Children's Hospital. Therefore, no claim for autism or autism spectrum disorder is being pursued in this litigation and no expert for Plaintiffs have claimed that M.B.D. has autism.

Therefore, the issue of whether or not M.B.D. has autism is *not* a fact of consequence to this litigation. Any such evidence is irrelevant and would not assist the trier of fact. If Dr. Wiznitzer is allowed to opine that minor M.B.D. does not have autism, it would serve only to unfairly prejudice Plaintiffs by giving the false impression that she is seeking compensation for injuries that minor M.B.D. did not actually suffer. *In re Baycol Prods. Litig.*, 532 F. Supp. 2d at 1067 (exclusion of testimony is appropriate where such testimony can cause jury confusion as to the nature of plaintiff's claims), *citing Bouchard v. Am. Home Prods. Corp.*, 213 F. Supp. 2d 802, 811 (N.D. Ohio 2002). Therefore, Dr. Wiznitzer's opinion that minor M.B.D. does not have autism should be excluded.

D. Motion To Exclude The Testimony Of Dr. Stephanie Greene

Plaintiff M.B.D. has been diagnosed with Chiari I malformation, a defect in which the cerebellum of the brain protrudes downward into the spinal column. Plaintiff's treating geneticist/dysmorphologist, Dr. Saal, attributes her Chiari I to Depakote. Abbott has retained a neurosurgeon, Dr. Stephanie Greene, to opine on whether Depakote, a known teratogen, caused M.B.D.'s Chiari I malformation. However, such opinions are outside the expertise of a neurosurgeon, and further Dr. Greene lacks an adequate basis to form this opinion. Therefore, such opinions must be excluded.

1. Dr. Greene Is Not Qualified To Opine On The Cause Of Plaintiff's Chiari

Dr. Greene is as a pediatric neurosurgeon. (Greene dep. 15:24-16:2, Doc.127, PageID

14940.) She is not a geneticist, teratologist, epidemiologist or dysmorphologist. (*Id.* at 15:1-16:2, Doc.127, PageID14940.) Dr. Greene cannot opine on the cause of M.B.D.'s Chiari I malformation because she is not "qualified by knowledge, skill, experience, training, or education" to determine the cause of birth defects. *See* Fed. R. Evid. 702. Etiology is the study of what caused the diagnosed disorder, as opposed to merely what the diagnosis is. *Tamraz v. Lincoln Elec. Co.*, 620 F.3d 665, 673 (6th Cir. Ohio 2010). An expert's ability "to diagnose medical conditions is not remotely the same … as the ability to deduce, delineate, and describe, in a scientifically reliable manner, the causes of those medical conditions." *Gass v. Marriott Hotel Servs.*, 558 F.3d 419, 426 (6th Cir. 2009) (citations omitted). Although Dr. Greene has clear qualifications as a neurosurgeon, she does not have medical expertise in etiology. In fact, Dr. Greene admits her lack of expertise. She testified that "to determine the extent of the effect valproic acid had on [M.B.D.] and her development," she would defer to a dysmporphologist or geneticist. (Greene dep. 51:3-10, Doc.127, PageID14949.)

While an expert may be qualified to testify in one area, that expert may be excluded from proffering opinions in another area. *Ullman v. Auto-Owners Mut. Ins. Co.*, 502 F. Supp. 2d 737, 743 (S.D. Ohio 2007). While Dr. Greene may be qualified to opine on the appropriateness of M.B.D.'s Chiari I surgery, she lacks qualifications to testify as to the cause of M.B.D.'s Chiari I.

2. Dr. Greene Has No Reliable Basis To Opine Whether Depakote Causes Chiari

Dr. Greene based her opinion that Depakote did not cause M.B.D.'s Chiari I upon her assumption that only one such case has been reported in the medical literature.[23] She was unaware of several other cases reported in the medical literature or included in Abbott's adverse event files. (Greene dep. 36:18-38:6, Doc.127, PageID14945.) She was unaware of published articles reporting Chiari I after teratogen exposure. (*Id.* at 41:4-11, Doc.127, PageID14946.)

[23] See Greene Ex. 2, Doc.127-1, PageID14963.

This incomplete understanding of the medical literature fails to establish "facts or data" sufficient to form a reliable opinion under Rule 702. *See In re Scrap Metal Antitrust Litig.*, 527 F.3d 517, 528-29 (6th Cir. 2008).

Additionally, Dr. Greene's methodology is unreliable. She testified that in forming her opinions on Chiari I causation: "I was only basing that on my own practice." (Greene dep. 41:13-18, Doc.127, PageID14946.) Dr. Greene testified that she records in utero exposure to medications when taking patient histories, but she does not recall hearing about Depakote exposure among her Chiari I patients. (*Id.* at 33:15-34:2, Doc.127, PageID14944.) Yet she testified she did not go back and review the medical records from her current practice to see if any patients had, in fact, reported in utero exposure to Depakote. (*Id.* at 40:20-24, Doc.127, PageID14946.) Further, she does not have access to records from her prior practice. Thus she bases her testimony upon purported data which she did not actually review or analyze, half of which was not even available. Dr. Greene's methodology therefore is not scientific or replicable.

To be a scientifically reliable methodology, an opinion must be based on "more than just subjective belief or unsupported speculation." *Daubert* 509 U.S. at 590. Dr. Greene's opinion, which she bases upon her claimed recollection of patients' records, does not satisfy any of the *Daubert* factors for reliability, which include replicable testing, peer review, known error rates, and acceptability in the relevant scientific community. *Kumho Tire Co.*, 526 U.S. at 145. Her testimony must therefore be excluded.

V. CONCLUSION

Plaintiffs respectfully request that this Honorable Court grant their motion to exclude the opinions and anticipated testimony of Abbott's experts, Dr. Kwame Anyane-Yeboa, Dr. Anthony Scialli, Dr. Max Wiznitzer, and Dr. Stephanie Greene as described above.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on February 17, 2015, I electronically filed this MOTION TO EXCLUDE PROFFERED EXPERT OPINIONS OF DR. KWAME ANYANE-YEBOA, DR. ANTHONY SCIALLI, DR. MAX WIZNITZER AND DR. STEPHANIE GREENE, AND MEMORANDUM IN SUPPORT THEREOF with the Clerk of the Court using the CM/ECF system, which will send notice of such filing to all counsel of record. Parties may access this filing through the Court's system.

/s/ Janet G. Abaray
Janet G. Abaray